Conclusion: Human FGFR1-IIIb-variant was shown to reduce tumor growth in vitro and in vivo and prolong overall survival.

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P41. RELEVANCE OF THE PTEN AND p27^{KIP1} EXPRESSION IN PROSTATE CANCER AFTER SHORT TERM ANTIHORMONAL THERAPY

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Background: PTEN is an important phosphatase, suppressing the phosphatidylinositol-3-kinase/Akt pathway which induces apoptosis. p27^{kip1} binds to cyclin-E/Cdk2 and prevents mitosis. The inactivation of the tumor suppressor genes has been associated with many different types of cancer including the prostatic carcinoma (PCa). In this study we investigated the influence of an antihormonal treatment on the expression of PTEN and p27^{kip1} in PCa.
Methods: 82 prostate cancer patients treated with antiandrogens or LH-RH analogs or a combination therapy between 1 and 77 weeks (mean 9.7 ± 1.2) were included in this study. The expression of PTEN and p27^{kip1} were analyzed by immunhistochemistry and an immunreactive score. The results were compared with 183 untreated cases of a previous study.
Results: PTEN expression levels correlated with the duration of antihormonal therapy: significantly more PTEN positive cases were found after 3 weeks antihormonal therapy ($p = 0.0003$). PTEN-expression compared to untreated tumors showed a significantly stronger PTEN-expression in treated tumors ($p = 0.03$). A nuclear expression of p27^{kip1} was more frequent in tumors after 4 weeks of treatment compared to tumors treated less than 4 weeks ($p = 0.015$).
Conclusions: Both PTEN and p27^{kip1} expression was increased after 4 weeks of antihormonal treatment. This fact might indicate an early stress reaction of the tumor cells due to the androgen-deprivation therapy.

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P42. GLYCOGEN SYNTHASE KINASE 3BETA (GSK3BETA) AS A KEY COMPONENT OF ESTRADIOL SIGNALLING PATHWAY

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Background: GSK3beta is involved in the control of gene expression via the regulation of transcription factors, including estrogen receptor alpha (ERalpha). Recently, we discovered involvement of GSK3beta in estrogen-independent and estrogen-dependent activation of ERalpha, respectively.[1,2] While phosphorylation of ERalpha appears to be crucial for its activation, the impact of GSK3beta on the estrogen-dependent regulation of ERalpha function and activity remains to be clarified.
Methods: Phosphorylation of ERalpha by GSK3beta was analysed by in vitro kinase assays. Thereafter, the effects of GSK3 inhibitors on ERalpha phosphorylation and activation were analysed in breast cancer cells using Western blot and luciferase reporter assays. Further experiments using siRNA technology and transfection of cells with GSK3beta mutants were performed to investigate the effects of GSK3beta regarding ERalpha signalling pathway.
Results: In vitro kinase assays first depicted that GSK3beta phosphorylated ERalpha at Ser-118. Moreover, the addition of a GSK3 inhibitor (LiCl) on MCF-7 cells in culture stimulated with estradiol (E2) led to a decrease in Ser-118 phosphorylation and to an inhibition of ERalpha-controlled luciferase activity. In agreement with the previous observations, the knock-down of GSK3 by use of siRNA resulted in decreased basal and E2-induced ERalpha phosphorylation at Ser-118 as well as in reduced luciferase activity.
Conclusion: We suggest that GSK3beta plays an important role in the estrogen-dependent regulation of ERalpha function and activity.

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P43. ErbB-SIGNALLING IN MULTIPLE MYELOMA – FROM THE IDENTIFICATION AS POTENTIAL THERAPEUTIC TARGET BY GENE EXPRESSION ANALYSIS AND FUNCTIONAL TESTING TO CLINICAL TRIALS

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Background: ErbB-receptors/ligands are involved in several cancers. Plasma cells expressing the heparin-sulphate proteoglycan (HSPG) syndecan-1 (CD138) attach heparin-binding growth factors.[1] The aim of this study is to identify new targets in the therapy of multiple myeloma (MM).
Methods: Samples of 65 patients (CD138-purified MM-cells (MMC) and bone-marrow-microenvironment (BMME)), 7 normal bone-marrow-plasma-cell-samples (BMPC) and 20 human-myeloma-cell-lines were studied. The expression of the 4 ErbB-receptors/ligands on MMC and BMME will be assessed by real-time RT-PCR and Affymetrix U133 A+B DNA-microarrays. BMME-cells from MM-patients were exposed to PD169540 (a pan-ErbB-inhibitor) and IRESSA (ErbB1-specific).
Results: ErbB1 and ErbB2 are expressed by BMPC, MMC and the BMME. ErbB3 and ErbB4 are expressed by a subgroup of MMC. 7/10 ErbB-ligands are expressed by MMC and/or the BBME. Myeloma cell growth is stimulated by the 3 ErbB-ligands that are able to attach HSPG (i.e amphiregulin, HB-EGF and neuregulin-1) via binding to syndecan-1. PD169540 and IRESSA induced apoptosis of primary MMC from 10/14 and 4/14 patients in vitro, respectively.[1,2]